R E M A R K S

The Office Action of January 15, 2002, presents the Examination of claims 1-6 and 21-22. Claim 2 is amended. Claims 23-25 are added. Support for said claims is found in the Sequence Listing. No new matter is inserted into the application.

Priority under 35 U.S.C. § 120

The Examiner states that the specification must be amended to refer to the parent application 08/998,549. Applicants point out that the specification was properly amended in the transmittal letter filed on July 3, 2001. In particular, the Examiner's attention is drawn to page 2, paragraph 5 of the transmittal letter. As such, the requirements under 35 U.S.C. § 120 are met, and the present application should receive priority to parent application 08/998,549. The Examiner is respectfully requested to acknowledge priority under 35 U.S.C. § 120 on the record.

Information Disclosure Statement (IDS)

The Examiner acknowledges the IDS filed on October 5, 2001. However, Applicants notice that two of the references listed on the Form PTO 1449 are crossed out. No reason is given for the crossing out of these references. The Examiner is respectfully requested to

consider these references and acknowledge such, or to explain why these references were not considered.

Objection to the disclosure

The Examiner objects to the disclosure for containing drawing material in the text, and recommends the cancellation of pages 22-23 of the specification. Applicants agree with the Examiner's suggestion since these pages have already been converted to Figure 1(A) and Figure 1(B), respectively, and amend the specification to delete pages 22 and 23. Thus the instant objection is overcome.

Objection to the claims

The Examiner objects to claim 2 for the misspelling of "immunogen." In response to the Examiner's remarks, Applicants amend the spelling in claim 2. Thus the instant objection is overcome.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 1-6 and 21-22 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner asserts that the phrase "partly but not wholly overlapping" in claim 1 is unclear. Applicants respectfully disagree. The phrase "overlapping peptides" is commonly used in this field of art, and thusly is clear to one of ordinary skill in the art. As evidence thereto, Applicants submit an article published in *Journal of Immunology* by C. Ebner et al., showing the use of such a phrase. Specifically, on page 1049, overlapping peptides are mentioned as a product that is possible to buy commercially.

The Examiner is reminded that definiteness of a claim under 35 U.S.C. § 112, second paragraph is analyzed in view of the claim interpretation that would be given by one of ordinary skill in the art. U.S. Pat. & Trademark Off., *Manual Pat. Examining Proc.* § 2173.02 (8th ed. 2001). The article above demonstrates that the meaning of "partly but not wholly overlapping" is clear to one of skill in the art such that claim 1 fully complies with the requirements of 35 U.S.C. § 112, second paragraph. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 1-6 and 21-22 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement, and claims

1-6 and 21-22 under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Enablement

The Examiner asserts that the specification does not enable an immunogen derived from *any* protein antigen comprising *any* fragment of *any* size. Applicants respectfully disagree for the following reasons.

Applicants address the "any protein" aspect of the rejection first. Examiner asserts that to derive an immunogen from a protein other than antigen birch pollen allergen Bet v 1 would constitute undue experimentation. In support of this argument, the Examiner argues that it is known in the art that a single amino acid change could have dramatic effects on protein function. However, the Examiner points to an article (Mikayama et al. PNAS, 90:10056-10060, 1993) that has nothing to do with allergens.

Contrary to the Examiner's assertions, it would not constitute undue experimentation for one of ordinary skill in the art to derive an immunogen from a protein other than antigen birch pollen allergen Bet v 1. For enablement, one skilled in the art must not

be required to perform undue experimentation in order to make and use any protein antigen, given the direction provided in the specification. Undue experimentation is generally seen as that which is excessive, and not commonly performed in the art. U.S. Pat. & Trademark Off., *Manual Pat. Examining Proc.* § 2164.01 (8th ed. 2001). As evidence thereto, Applicants submit the following review articles, which demonstrate that the methods for preparing proteins and peptides where known prior to the instant filing date: O. Scheiner et al. (*Arbeiten aus dem Paul-Ehrlich-Institut*, 1994), Stiege et al. (*J. of Biotechnology* 41:81-90, 1995), and O. Scheiner (*Int. Arch. Allergy. Immunol* 98:93-96, 1992).

Each of these articles describes the preparation of proteins and peptides derived from a known immunogen as routine. For example, Scheiner et al. states, "By applying recombinant DNA techniques [well-defined allergen preparations] can be achieved with respect to both, characterization and reproducibility of allergen preparations." O. Scheiner et al. at p. 1. Stiege et al. states, "With the exchange of a single amino acid…, it will be possible to create proteins with better or even new biological activities," suggesting that amino acid modification is routine in the art. Stiege et al. at p. 88. Scheiner fully describes the technical aspects of producing a recombinant allergen on page 94.

These articles provide evidence that in the art of protein allergen research, contrary to the Examiner's assertions, it would be routine, rather than undue, experimentation to make the claimed immunogen from any protein allergen, given the guidance provided in the instant specification.

Next, Applicants respond to the "*any* fragment of *any* size" aspect of the rejection. Applicants emphasize that because the function of the fragments is recited in the claims, any non "non-anaphylatic" fragments are not encompassed by the scope of the claims. Thus, the claims do not encompass any fragment of any size, but only those that are derived from a protein allergen and are non-anaphylactic. In any event, the Examiner provides no proof or reasoning to doubt that a fragment of *any* size would retain the function recited in the claims. For this reason, Applicants submit that the Examiner has not made a *prima facie* case of lack of enablement.

As noted above, there is sufficient guidance and direction in the art as to how the skilled artisan could make and use allergen peptides. Further, the structural and functional characteristics of an immunogen are disclosed in the specification, such as on page 3, line 24 to page 4, line 3, and page 5, line 37 to page 6, 1. For all of these reasons, the skilled artisan is readily able to

make and use the claimed immunogens based the combination of knowledge in the art and the guidance provided in the specification. Withdrawal of the instant rejection is therefore respectfully requested.

Written Description

For written description, there must be enough examples (i.e. "species") in the specification to describe a "genus" of proteins. The Examiner asserts that the disclosure of three immunogens (SEQ ID NOs: 19-21) does not adequately describe the genus of immunogens claimed. Applicants respectfully disagree, and submit that the disclosure of Bet v 1 is sufficient description to represent an immunogen derived from any protein. As noted above, the structural and functional characteristics of an immunogen are disclosed in the specification, such as on page 3, line 24 to page 4, line 3, and page 5, line 37 to page 6, 1. The disclosure of Bet v 1 allergen is only an example, not a limitation, of the invention.

For all of these reasons, the instant specification reasonably conveys to one skilled in the art that the Inventors were in possession of the claimed invention. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 102(b)

Vrtala et al.

The Examiner rejects claims 1-2, 4, and 6 under 35 U.S.C. § 102(b) for allegedly being anticipated by Vrtala et al. (*J. Clin. Immunol.* 98:913-921, 1996). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Vrtala et al. is asserted to teach a dimeric form of recombinant Bet v 2, which is reactive with IgE but not IgE in 4 out of 6 animals. The Examiner asserts that since IgE is required for anaphylactic shock to allergen and since the recombinant Bet v 2 of Vrtala et al. showed little reaction to IgE, the protein would be non-anaphylactic. Applicants respectfully disagree.

The present invention is drawn to an immunogen derived from a protein allergen, which comprises

a) a non-anaphylactic immunogenic recombinant fragment of the protein allergen, which contains an IgG epitope partly, but not wholly, overlapping an IgE epitope;

b) a polymeric form of the fragment, in which form the fragment constitutes the monomeric units; or

c) a non-anaphylactic recombinant polymeric form of the protein allergen having 2 to 10 monomeric units, in which the protein allergen constitutes the monomeric units.

Vrtala et al. discloses that recombinant Bet v 2 (rBet v 2), which is an allergen distinct from Bet v 1, gave rise to lower IgE responses and induced more IgG than Bet v 1 after immunization in mice. The authors of Vrtala et al. interpreted the difference in immunogenicity and reduced ability to induce IgE antibodies as being due to polymer formation because the Bet v 2 was able to form oligomers via disulfide bonds.

The Examiner interprets the results of Vrtala et al. as being indicative that the Bet v 2 protein would be a non-anaphylactic immunogen. However, the Examiner appears to be misinterpreting the reduced ability to induce an IgE response after immunization as equating to a reduced capacity to induce an allergic or anaphylactic response in a host who is sensitized and thus already has specific IgE antibodies. Vrtala et al. are looking at the primary IgE response from an initial immunization with the Bet v 2 protein. This response is not indicative of whether or not the same protein would be anaphylactic or not in an animal which already has the necessary specific IgE antibodies.

Enclosed herewith is a copy of an article by Pauli et al. (*J. Allergy Clin. Immunol.* 97 1100-1109 (1996)) wherein it was clearly demonstrated that the same recombinant Bet v 2 of Vrtala et al., induces immediate-type skin reactions in patients expressing rBet v 2-IgE. Thus, Pauli et al. clearly evidence that the Bet v 2 protein of Vrtala et al. is not a non-anaphylactic immunogen and as such is outside the scope of the present invention. The present invention is, therefore, not anticipated by Vrtala et al. Withdrawal of the rejection is respectfully requested.

Rogers et al. Maintain

The Examiner rejects claims 1-2, 4, and 6 under 35 U.S.C. § 102(b) for allegedly being anticipated by Rogers et al. (*Mol. Immunol.* 31(13):955-966, 1994). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

As noted above, the claimed immunogen of the present invention comprises a non-anaphylactic immunogenic recombinant fragment of the protein allergen, which contains an IgG epitope partly, but not wholly, overlapping an IgE epitope. Rogers et al. discloses recombinant proteins comprised of peptides containing recombined T cell epitopes. However, Rogers et al. fails to disclose an IgG

epitope on the recombinant proteins, and therefore fails to anticipate the present invention. Withdrawal of the rejection is therefore respectfully requested.

Ebner et al.

The Examiner rejects claims 1-2 and 4-5 under 35 U.S.C. § 102(b) for allegedly being anticipated by Ebner et al. (*J. Immunol.* 150:1047-1054, 1993). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Ebner et al. is asserted to teach recombinant Bet v 1 peptides which elicit a T cell response, but which do not have an IgE epitope. The Examiner asserts that the peptides of Ebner et al. differ from the present peptides only in whether they contain an IgG epitope and are non-anaphylactic, and that the burden is upon Applicants to establish whether such differences exist. In response thereto, Applicants note that C. EBNER, R. VALENTA and D. KRAFT, co-authors of Ebner et al., are also co-inventors of the present invention. As indicated by the enclosed executed Declaration submitted under 37 C.F.R. § 1.132, the peptides of Ebner et al. only contain T cell epitopes and do not have binding sites for antibodies, i.e. do not have an IgG epitope. As such, the present

invention is not anticipated by Ebner et al. Withdrawal of the rejections is therefore respectfully requested.

Vrtala et al. Maintain

The Examiner rejects claims 1-2 and 4-5 under 35 U.S.C. § 102(a) for allegedly being anticipated by Vrtala et al. (*J. Clin. Invest.* 99(7):1674-1681, 1997). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that the peptides of Vrtala et al. differ from the present peptides only in whether they contain an IgG epitope and are non-anaphylactic, and that the burden is upon Applicants to establish whether such differences exist. In response thereto, Applicants note that S. VRTALA, the first author of Vrtala et al., is also a co-inventor of the present invention. Applicants are in the process of preparing a Declaration submitted under 37 C.F.R. § 1.132 to be executed by S. Vrtala, stating that the peptides disclosed therein do not have an IgG epitope. As such, the present invention is not anticipated by Vrtala et al. and the instant rejection will be overcome.

Rejections under 35 U.S.C. § 103(a)

Applicants respectfully traverse the remaining rejections under 35 U.S.C. § 103(a) presented in paragraphs 19-25 of the outstanding Office Action. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Regarding the combination of Vrtala et al. and Rogers et al. presented in paragraph 19, the use of a peptide linker is moot since neither reference discloses or suggests an IgG epitope on the recombinant proteins.

Regarding the combination of Vrtala et al. and U.S. Patent 4,269,764 presented in paragraph 20, the use of a polymerized antigen is moot since neither reference discloses an IgG epitope on the recombinant proteins.

Regarding the combination of Vrtala et al., U.S. Patent 4,269,764, and U.S. Patent 4,629,783 presented in paragraph 21, the use of a peptide linker is moot since none of the references disclose or suggest an IgG epitope on the recombinant proteins.

Regarding the combination of Ebner et al. and U.S. Patent 4,269,764 presented in paragraph 22, the use of a polymerized antigen is moot since neither reference discloses an IgG epitope on the recombinant proteins.

Regarding the combination of Ebner et al., U.S. Patent

4,269,764, and U.S. Patent 4,629,783 presented in paragraph 23, the use of a peptide linker is moot since none of the references disclose an IgG epitope on the recombinant proteins.

Regarding the combination of Ebner et al., Vrtala et al., U.S. Patent 4,269,764, U.S. Patent 4,629,783, and U.S. Patent 6,126,939 presented in paragraph 24, the use of a peptide linker is moot since none of the references disclose an IgG epitope on the recombinant proteins.

Finally, regarding the combination of Vrtala et al., Rogers et al, U.S. Patent 4,629,783, and U.S. Patent 6,126,939 presented in paragraph 25, the use of a peptide linker is moot since none of the references disclose an IgG epitope on the recombinant proteins.

Conclusion

As the above-presented amendments and remarks address and overcome the rejections of the Examiner, withdrawal of the rejections and reconsideration and allowance of the claims are respectfully requested. Should the Examiner have any questions regarding the present application, the Examiner is requested to contact Kristi L. Rupert, PhD (Reg. No. 45,702) in the Washington DC area, at (703) 205-8000.

Pursuant to 37 C.F.R. §§1.17 and 1.136(a), Applicants respectfully petition for a one (1) month extension of time filing a response in connection with the present application and the required fee of $110.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments:

1) C. Ebner et al., J Immunol (1993), 150:3, p. 1047-54
2) O. Scheiner et al., Arbeiten aus Paul-Ehrlich-Institut (1994), Gustav Fischer Verlag, p. 221-234
3) W. Stiege et al., J Biotechnol (1995) 41, p. 81-90
4) O. Scheiner, Int Arch allergy Immunol (1992), 98, p. 93-96
5) Pauli et al., J. Allergy Clin. Immunol. (1996) 97:1100-11-9
6) Declaration Under 37 C.F.R. §1.132

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Pages 22 and 23 of the specification have been deleted in their entirety, and the remaining pages have been renumbered starting with page 22.

In the Claims:

The claims have been amended as follows:

2. (Twice Amended) The immunogen [immogen] according to claim 1, wherein the polymeric form of said fragment is recombinantly produced.

Claims 23-25 have been added.